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RESEARCH ARTICLE

Evaluating the updated LATE-NC staging criteria using data from NACC

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Abstract

INTRODUCTION: Limbic-predominant age-related TAR DNA-binding protein of 43 kDa encephalopathy neuropathologic change (LATE-NC) staging criteria were updated in 2023. We evaluated this updated staging using National Alzheimer's Coordinating Center data.

METHODS: We examined associations of LATE-NC stages with cognition and other neuropathologic changes (NCs), and with cognition while accounting for other NCs, using multilevel regression models.

RESULTS: Of 1352 participants, 502 (37%) had LATE-NC (23% stage 1a, 6% stage 1b, 58% stage 2, 13% stage 3). LATE-NC stages were associated with cognition, hippocampal sclerosis of aging (HS-A), Alzheimer's disease NC (ADNC), Lewy bodies (LBs), and hippocampal atrophy. While stage 1b was associated with cognition and HS-A consistent with other stages, it was not associated with ADNC or LBs. All LATE-NC stages remained significantly associated with worse cognition when accounting for other NCs.

DISCUSSION: The updated LATE-NC staging criteria capture variations in early TDP-43 pathology spread which are consequential for cognition and associations with other NCs.

KEYWORDS
Alzheimer's disease, amygdala, dementia, hippocampal sclerosis of aging, hippocampus, limbic predominant age-related TAR DNA-binding protein of 43 kDa encephalopathy neuropathologic change, National Alzheimer's Coordinating Center, neuropathology

Highlights

- We applied the updated limbic-predominant age-related TAR DNA-binding protein of 43 kDa encephalopathy neuropathologic change (LATE-NC) staging criteria to data from the National Alzheimer's Coordinating Center.

- LATE-NC stage 1b was identified in 22% of participants with stage 1.
- In contrast to other LATE-NC stages, stage 1b was not associated with Alzheimer's disease neuropathologic change (ADNC) or Lewy bodies.
- Stages 1a and 1b were significantly associated with dementia and memory impairment.
- Stages 1b+ were more strongly tied to dementia than all other neuropathologic changes except high likelihood ADNC.

1 | BACKGROUND

Pathological TAR DNA-binding protein of 43 kDa (TDP-43) was first discovered in the context of amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD).[1,2] However, the context in which pathological TDP-43 deposition is most commonly found is among older individuals, where it is consistently and strongly associated with dementia of the Alzheimer's disease (AD) type.[3–6] This TDP-43 pathology in older age was coined as limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC) in 2019,[7] providing a common language for researchers to further study and communicate findings regarding this TDP-43 deposition in older age. The 2019 LATE-NC paper also included a recommended staging scheme which consisted of three stages positing TDP-43 deposition began in the amygdala (stage 1), proceeded to the hippocampus (stage 2), and finally reached the middle frontal gyrus for stage 3. While this staging scheme has proved useful for capturing the majority of patterns of LATE-NC TDP-43 deposition, variations outside of this original staging scheme have been reported.[8–11] In particular, some participants exhibit TDP-43 accumulation in the hippocampus without TDP-43 being detected in the amygdala; according to strict enforcement of the 2019 criteria this would not be classified as LATE-NC, though in practice many studies have effectively treated these cases as LATE-NC stage 2.

In 2023, updated LATE-NC criteria were released which addressed this issue of differences in the spread of TDP-43 pathology across regions affected early in the disease process, and also provided further criteria to help differentiate LATE-NC from ALS and FTLD-related TDP-43 (FTLD-TDP) and highlighted other forms of TDP-43 pathology deposition which rule out LATE-NC.[12] The updated LATE-NC staging criteria has recommended evaluating the spread of TDP-43 based on histology slides taken from the anatomical regions of the amygdala, hippocampus, and middle frontal gyrus: LATE-NC stage 1 is defined as the presence of TDP-43 inclusions on the slide from the amygdala region or the slide from the hippocampal region, while LATE-NC stage 2 is defined as TDP-43 neuronal cytoplasmic inclusions (NCIs) present in both the amygdala and hippocampus, and stage 3 is defined as TDP-43 NCIs present in each of the amygdala, hippocampus, and middle frontal gyrus. This new definition of stage 1 also includes a subtype system, in which TDP-43 in the amygdala only is classified as stage 1a while TDP-43 in the hippocampus only is classified as stage 1b. However, the significance of the updated LATE-NC staging criteria has not yet been established.

We sought to evaluate the updated LATE-NC staging criteria, including the stage 1 subtype system, in relation to clinical diagnosis, other neuropathologic changes (NCs), and other autopsy findings, in participants from the National Alzheimer's Coordinating Center (NACC) neuropathology database. NACC aggregates data from > 40 Alzheimer's Disease Research Centers (ADRCs), including standardized clinical and cognitive assessments and neuropathology forms. Specifically, we used data from version 10 or later neuropathology forms,[13,14] which include fields for the assessment of TDP-43 in the amygdala, hippocampus, and neocortex, to classify participants according to the updated LATE-NC staging criteria, compare clinical diagnosis and other NCs across LATE-NC stages, and examine the impact of the different LATE-NC stages on clinical diagnoses while accounting for related NCs.

2 | METHODS

2.1 | Participant selection

We used information from autopsy participants in the NACC database (through the March 2023 data freeze) who had version 10 or later neuropathology[13] and Uniform Data Set (UDS) assessments available.[15] Contributing ADRCs are approved by their local institutional review board. We used information from both the neuropathology data and from the last visit for our inclusion and exclusion criteria. To assign the updated LATE-NC staging criteria, we selected participants who had TDP-43 assessments from the amygdala, hippocampus, and neocortex. To focus on the most appropriate population for LATE-NC, we excluded participants who had certain rare NCs. Briefly, we excluded those with FTLD-TDP or ALS (with or without TDP-43), those who had certain types of FTLD-tau, and other rare NCs. We also excluded participants with neocortical TDP-43 who did not have inclusions in either the amygdala or hippocampus as this is another exclusionary criterion for LATE-NC according to the updated staging criteria. A full list of excluded NCs is described in the Supplementary Methods in supporting information. We also excluded those with

a frontotemporal dementia (FTD)-related mutation or a dominantly inherited AD mutation, noted in either the neuropathology forms or the UDS forms.

Because LATE-NC is primarily associated with an amnestic form of dementia and it is in this context in which a better understanding of LATE-NC is most needed,[16] we selected participants with a primary etiologic diagnosis of AD or who were unimpaired at their last visit. The etiological diagnosis of AD in NACC is based on the 2011 National Institute on Aging (NIA) Alzheimer's Association (AA) criteria for AD dementia[17] or mild cognitive impairment (MCI) due to AD.[18] Notably these criteria do not incorporate biomarker results but rather are meant to capture dementia "of the Alzheimer's type" in which a primarily amnestic syndrome with memory as first presentation is the most common form. Thus, by concentrating on those with an etiological diagnosis of AD or without impairment, we are trying to focus on the most clinically relevant group for LATE-NC as well as exclude participants with other clinical etiologic diagnoses that might be related to other TDP-43 pathologies. While strongly related, clinical AD is not always related to underlying ADNC,[19] but is the most common phenotype of both ADNC and LATE-NC. Furthermore, we believe focusing on a more clinically homogeneous group provides a stronger validation of the updated LATE-NC criteria, especially the more controversial stage 1 subtyping system.

Last, because of the uncertainty in the definition of the entorhinal cortex/inferior temporal cortex (EC/ITC) region in the neuropathology forms, this assessment can only be used to assign LATE-NC stage 1 by the updated criteria but cannot be used for assigning stage 1 subtypes. Because of this uncertainty, we excluded participants with isolated TDP-43 in the EC/ITC region (i.e., no amygdala or hippocampal TDP-43 found).

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (e.g., PubMed) sources. Studies have yet to report on the distribution of stages or associations with co-occurring pathologies or clinical diagnosis for the updated limbic-predominant age-related TAR DNA-binding protein of 43 kDa (TDP-43) encephalopathy neuropathologic change (LATE-NC) staging criteria. Other LATE-NC staging systems are discussed in the article.
2. **Interpretation**: Our findings suggest that different patterns of early TDP-43 spread in LATE-NC, as captured by the updated criteria, are associated differently with co-occurring pathologies. This may relate to potential mechanisms of general pathological misfolded protein accumulation. All LATE-NC stages were nonetheless consequential for cognitive outcomes.
3. **Future directions**: Studies with more specific TDP-43 assessments can validate and qualify the findings from our study by identifying more precise amygdala and hippocampal regions and types of TDP-43 inclusions involved in early LATE-NC stages. The amygdala as a locus for the accumulation of different misfolded proteins, as reinforced by our findings, merits further investigation.

2.2 | Demographic variables

We used demographic and clinical diagnosis information from the last visit before death. For demographic information, we used age at death, sex, years of education, and the interval between the last visit and death. We also report the presence of an apolipoprotein E (*APOE*) ε4 allele as available in the NACC genetic data. We used information from the cognitive status either as a three-point scale (dementia, MCI or questionable cognitive impairment [QCI], or no impairment, with MCI and QCI assigned to the same category due to the low frequency of QCI) for ordinal models, or dichotomized by dementia, or dichotomized by impairment (no impairment vs. QCI/MCI/dementia). We also used the Clinical Dementia Rating (CDR®) Dementia Staging Instrument memory scores, either the full scale for ordinal models or dichotomized as mild impairment or greater.

2.3 | Assigning LATE-NC stages

While strict adherence to the updated LATE-NC stage criteria using NACC data is not possible, we took the variables for TDP-43 inclusions in the amygdala, hippocampus, and neocortex to assign LATE-NC stages as best could be applied. As illustrated in Figure 1, stage 1 was defined as the presence of TDP-43 in the amygdala only (stage 1a) or hippocampus only (stage 1b). Stage 2 was defined as the presence of TDP-43 in both the amygdala and the hippocampus, but not the neocortex. Stage 3 was defined as TDP-43 in the amygdala, hippocampus, and neocortex. We discuss the EC/ITC TDP-43 variable in the Supplementary Methods.

2.4 | Other NCs and autopsy findings of interest

We used information regarding other common NCs and autopsy findings, assessed using standard guidelines.[20,21] For variables with multiple levels, we analyzed dichotomized as well as ordinal versions. Variables with multiple levels included AD neuropathologic change (ADNC) as well as the global vascular NCs of cerebral amyloid angiopathy (CAA), atherosclerosis, arteriolosclerosis, and gross measures of hippocampal and cortical atrophy. We used the following levels for the dichotomized version of these variables: ADNC as none/low vs. intermediate/high likelihood, and CAA, atherosclerosis, arteriolosclerosis, gross hippocampal atrophy, and gross cortical atrophy, as none/mild vs. moderate/severe. For Lewy bodies (LBs), we examined both a dichotomized version in which any LBs (brainstem, amygdala predominant, limbic transitional, neocortical, or olfactory bulb) indicated

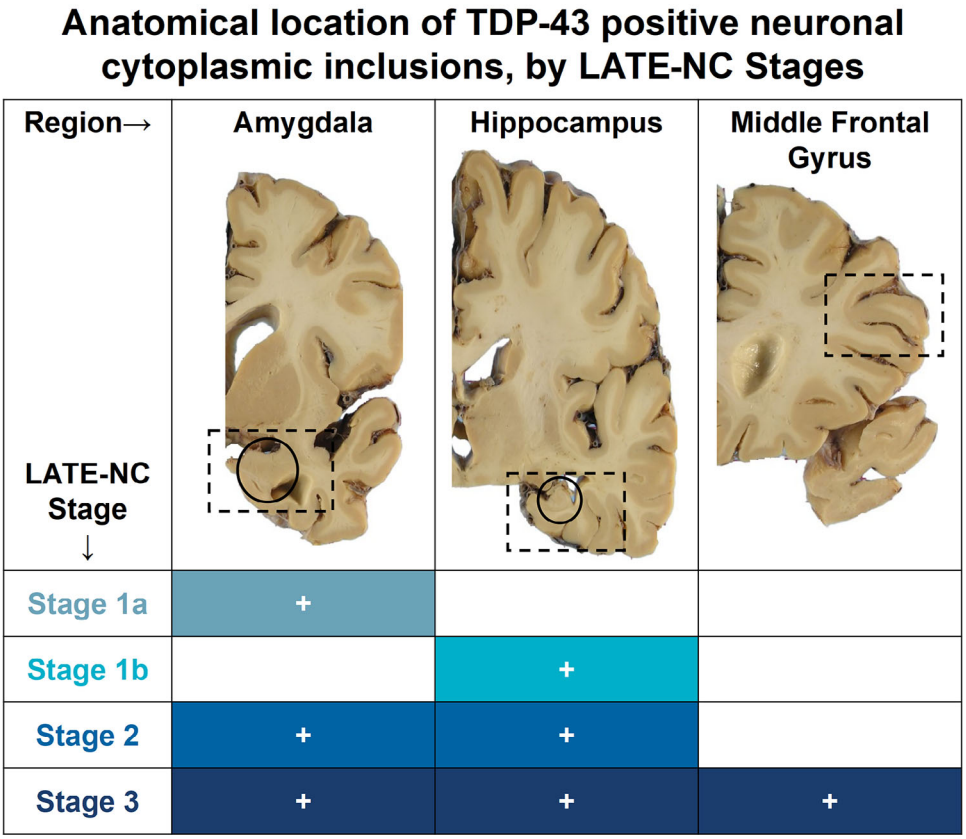

FIGURE 1 Illustration of updated LATE-NC staging system as applied to NACC neuropathology data in this study. Presence of TDP-43 neuronal cytoplasmic inclusions for different brain regions by LATE-NC stage, including stage 1 subtypes (1a and 1b). Stage 1a denotes TDP-43 inclusions found only in the amygdala but not the hippocampus or middle frontal gyrus, while stage 1b denotes TDP-43 inclusions found only in the hippocampus but not the amygdala or the middle frontal gyrus. Stage 2 denotes TDP-43 inclusions found in the amygdala and hippocampus but not the middle frontal gyrus, while stage 3 denotes TDP-43 inclusions found in all three regions. LATE-NC, limbic-predominant age-related TDP-43 encephalopathy neuropathologic change; NACC, National Alzheimer's Coordinating Center; TDP-43, TAR DNA-binding protein of 43 kDa.

presence, and we also examined the following LB subtypes: amygdala predominant, limbic, neocortical, or olfactory bulb/brainstem. We classified hippocampal sclerosis of aging (HS-A) as present if any HS-A was noted, regardless of laterality. We also used the assessment of gross frontal/temporal lobar atrophy, which was available as present vs. absent. Finally, we used data regarding the presence of the following localized vascular NCs: old gross infarcts, old microinfarcts, old gross hemorrhages, old microhemorrhages, acute/subacute gross infarcts, acute/subacute microinfarcts, acute/subacute gross hemorrhages, and acute/subacute microhemorrhages.

2.5 | Statistical analyses

2.5.1 | Participant characteristics

To examine differences in participant characteristics concerning LATE-NC stages, we report Kruskal–Wallis rank-sum tests for continuous variables and chi-square tests for categorical variables, across all categories. For simplicity, we report dichotomized versions of the variables in the main text (Table 1) but provide the full scores in Table S1 in supporting information where we also report the number of missing values for each variable by LATE-NC stage and perform comparisons between each successive level (no TDP-43 vs. stage 1a, 1a vs. 1b, 1b vs. 2, and 2 vs. 3) using Wilcoxon rank-sum tests for continuous variables and chi-square tests for categorical variables.

2.5.2 | Associations of LATE-NC stages with clinical diagnoses and other NCs

To examine the association of LATE-NC stages with clinical diagnoses, other NCs, and gross assessments of atrophy at autopsy, we performed regressions adjusting for age at death, sex, years of education, and the interval between last visit and death. We used binomial logistic regressions for dichotomized versions of the variables and ordinal logistic regressions for ordinal versions. When examining associations of LATE-NC with LBs by their subtypes, we performed logistic regressions in which each LB subtype was compared to those without LBs (i.e., participants with other types of LBs were excluded from the model). To compare the associations with clinical diagnoses and other NCs between the LATE-NC stages we performed post hoc tests for the

TABLE 1 Participant characteristics.

Characteristic	No LATE-NC, $N = 850$[a]	Stage 1a, $N = 115$[a]	Stage 1b, $N = 32$[a]	Stage 2, $N = 291$[a]	Stage 3, $N = 64$[a]	p value[b]
Age at death (years)	82.0 (10.6)	81.4 (9.6)	85.7 (8.7)	85.5 (8.9)	88.6 (7.4)	<0.001
Sex						0.2
Female	446 (52%)	67 (58%)	18 (56%)	175 (60%)	32 (50%)	
Male	404 (48%)	48 (42%)	14 (44%)	116 (40%)	32 (50%)	
Education (years)	15.7 (3.0)	15.2 (3.1)	16.4 (2.7)	15.8 (3.0)	15.9 (2.9)	0.3
Last visit to death (years)	2.2 (2.4)	2.6 (2.7)	2.5 (2.7)	2.4 (2.5)	3.4 (3.2)	0.008
APOE ε4						<0.001
Absent	416 (54%)	44 (40%)	10 (34%)	106 (40%)	26 (44%)	
Present	360 (46%)	67 (60%)	19 (66%)	161 (60%)	33 (56%)	
TDP-43 antibody						0.3
Phospho-specific	632 (75%)	91 (80%)	27 (84%)	232 (80%)	47 (73%)	
Non–phospho-specific	210 (25%)	23 (20%)	5 (16%)	58 (20%)	17 (27%)	
No TDP-43	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Cognitive status						<0.001
Normal	220 (26%)	14 (12%)	6 (19%)	10 (3.4%)	2 (3.1%)	
MCI/impaired	87 (10%)	5 (4.3%)	1 (3.1%)	20 (6.9%)	2 (3.1%)	
Dementia	543 (64%)	96 (83%)	25 (78%)	261 (90%)	60 (94%)	
CDR-SB	7.9 (6.8)	10.4 (6.0)	10.5 (6.6)	11.7 (5.7)	10.5 (5.7)	<0.001
Memory impairment						<0.001
Absent	308 (36%)	19 (17%)	5 (16%)	31 (11%)	6 (9.4%)	
Present	542 (64%)	96 (83%)	27 (84%)	260 (89%)	58 (91%)	
HS-A						<0.001
Absent	796 (95%)	101 (89%)	21 (68%)	183 (63%)	24 (38%)	
Present	46 (5.5%)	13 (11%)	10 (32%)	106 (37%)	39 (62%)	
ADNC						<0.001
None/low	223 (26%)	13 (11%)	9 (28%)	33 (11%)	6 (9.4%)	
Intermediate/high	620 (74%)	102 (89%)	23 (72%)	257 (89%)	58 (91%)	
CAA						0.024
None/mild	550 (65%)	67 (58%)	20 (65%)	172 (59%)	29 (46%)	
Moderate/severe	300 (35%)	48 (42%)	11 (35%)	119 (41%)	34 (54%)	
LBs						<0.001
Absent	547 (65%)	42 (37%)	25 (78%)	133 (46%)	29 (45%)	
Present	300 (35%)	73 (63%)	7 (22%)	158 (54%)	35 (55%)	
Atherosclerosis						0.003
None/mild	527 (63%)	68 (60%)	21 (66%)	147 (51%)	31 (48%)	
Moderate/severe	316 (37%)	45 (40%)	11 (34%)	142 (49%)	33 (52%)	
Arteriolosclerosis						<0.001
None/mild	435 (52%)	53 (48%)	13 (42%)	108 (40%)	18 (29%)	
Moderate/severe	395 (48%)	57 (52%)	18 (58%)	164 (60%)	45 (71%)	
Gross hippocampal atrophy						<0.001
None/mild	494 (60%)	50 (44%)	14 (44%)	99 (34%)	14 (23%)	
Moderate/severe	335 (40%)	63 (56%)	18 (56%)	190 (66%)	47 (77%)	

(Continues)

TABLE 1 (Continued)

Characteristic	No LATE-NC, $N = 850$[a]	Stage 1a, $N = 115$[a]	Stage 1b, $N = 32$[a]	Stage 2, $N = 291$[a]	Stage 3, $N = 64$[a]	p value[b]
Gross cortical atrophy						0.007
None/mild	484 (60%)	58 (51%)	18 (58%)	135 (48%)	31 (51%)	
Moderate/severe	323 (40%)	55 (49%)	13 (42%)	146 (52%)	30 (49%)	
Gross lobar atrophy						0.2
Absent	648 (80%)	92 (81%)	21 (68%)	217 (77%)	53 (87%)	
Present	159 (20%)	21 (19%)	10 (32%)	64 (23%)	8 (13%)	

Abbreviations: ADNC, Alzheimer's disease neuropathologic change; *APOE*, apolipoprotein E; CAA, cerebral amyloid angiopathy; CDR-SB, Clinical Dementia Rating Sum of Boxes; HS-A, hippocampal sclerosis of aging; LATE-NC, limbic-predominant age-related TDP-43 encephalopathy neuropathologic change; LB, Lewy bodies; MCI, mild cognitive impairment; SD, standard deviation; TDP-43, TAR DNA-binding protein of 43 kDa.
[a]Mean (SD); *n* (%).
[b]Kruskal–Wallis rank-sum test; Pearson chi-squared test.

following preselected comparisons between stages: 1a versus 1b, 1a versus 2, 1b versus 2, and 2 versus 3.

2.5.3 | Associations of LATE-NC stages with clinical diagnoses while accounting for other NCs

To examine the effect of LATE-NC on clinical diagnoses while accounting for related NCs, we examined cognitive diagnosis and CDR memory scores with regards to LATE-NC stages using regressions accounting for age, sex, education, the interval between last visit and death, as well as the other NCs. We examined dichotomized versions (dementia, mild memory impairment or greater) using logistic regressions and full scores using ordinal logistic regressions.

2.5.4 | Additional statistical analysis details and software

Because NACC aggregates data across many contributing ADRCs, we used multilevel models with a varying intercept for center for all our analyses. Initial examination of the dichotomized outcomes concerning LATE-NC stages suggested multilevel models with varying intercepts by center fit the data best (lower Akaike information criterion values) compared to both models that did not account for center and multilevel models with both varying intercepts for center and varying slope for LATE-NC by center (data not shown). For logistic regression multilevel models we used the glmer function, with binomial distribution and logit link function, from the lme4 package,[22] while for ordinal logistic regression multilevel models we used the clmm function, with binomial distribution and cumulative logit link function, from the ordinal package.[23] To improve convergence, continuous predictors (age, years of education, time from last visit to death) were mean-centered and scaled by the standard deviation (i.e., *z* score normalized) in the regression models. For conducting our preselected post hoc comparisons across the different LATE-NC stages we used the emmeans package.[24]

Participant characteristic tables and comparisons were generated using the gtsummary package,[25] while graphs summarizing the final regression models for cognitive status and CDR memory scores while accounting for other NCs were generated using the ggstats package.[26] For all analyses we performed complete case analyses and reported unadjusted *p* values. All analyses were performed using R statistical software (v4.3).

3 | RESULTS

3.1 | Participant characteristics

We started with 7476 participants with neuropathology data available, of which 4326 (58%) had version 10 or higher neuropathology forms, and of these 2451 (57%) had TDP-43 regional assessments for the amygdala, hippocampus, and neocortex. We then excluded 674 participants (27.5%) due to the presence of exclusionary NCs. Last, we excluded 425 (23.9%) of the remaining participants who either had a non-AD etiologic diagnosis for their cognitive impairment ($n = 410$) or had isolated TDP-43 in the EC/ITC region ($n = 15$). This resulted in a total of 1352 participants coming from 33 different ADRCs. We show the inclusion/exclusion flow diagram in Figure S1 in supporting information.

Participant characteristics are shown by LATE-NC stages in Table 1, with the full distribution of scores shown in Table S1. The overall sample consisted of 614 men (45%) and 738 women (55%), and the mean age at death was 83 ± 10 years. Briefly, 502 participants, or 37%, were classified as having LATE-NC, of which 147 (29%) were classified as stage 1, 291 (58%) as stage 2, and 64 (13%) as stage 3. Of those with LATE-NC stage 1, 32 (22%) were stage 1b. These participants with stage 1b came from 14 different ADRCs. Ages at death increased with increasing LATE-NC stage: those without LATE-NC died on average at 82.0 years of age, while those with LATE-NC stage 1a died on average at 81.4 years, stage 1b at 85.7 years, stage 2 at 85.5 years, and those with stage 3 at 88.4 years. Of note, the average age at death was

not different between those without LATE-NC and those with LATE-NC stage 1a but was significantly different between stage 1a and 1b ($p = 0.028$, Table S1). There were no significant differences between groups with regard to sex. Years of education only significantly differed between stage 1a and 1b with stage 1b having more years of education on average ($p = 0.041$, Table S1). LATE-NC stage 3 was associated with a longer interval from the last visit to death. Participants with LATE-NC more commonly possessed an *APOE* ε4 allele (≈ 60%) compared to those without LATE-NC (46%), though there was no apparent difference in *APOE* ε4 frequency between the LATE-NC stages. With regard to the type of TDP-43 antibody used for assessment, a phospho-specific antibody was used in 75% of participants without LATE-NC, while this percentage was slightly higher in those with LATE-NC stages 1a–2 (85%–80%) but similar to those with LATE-NC stage 3 (73%). As a follow-up, we compared the frequency at which phospho-specific TDP-43 antibody was used between those without and those with LATE-NC (i.e., no LATE-NC vs. stages 1a–3 grouped), which showed a trend toward more frequent assessment with a phospho-specific TDP-43 antibody in those with LATE-NC ($p = 0.072$, chi-square test). In examining ADRC-specific trends, individual centers were generally consistent in which type of TDP-43 antibody they used: out of 33 ADRCs, 19 (58%) only used phospho-specific TDP-43, 8 (24%) used non–phospho-specific TDP-43 (resulting in a total of 82% that only used one or the other), 3 (9%) mostly used one or the other (in 90% or more of their participants), and only 3 (9%) had a mix of participants assessed with either non–phospho-specific or phospho-specific TDP-43.

While examined in closer detail in statistical models in the following sections, we briefly outline findings concerning clinical diagnoses, other NCs, and gross atrophy findings. Participants with LATE-NC more often had cognitive impairment, dementia, and memory problems, compared to those without LATE-NC. The frequency of these cognitive problems increased with increasing stage, though stages 1a and 1b were largely similar in this regard. The frequency of neurodegenerative and global vascular NCs was more common in those with LATE-NC. With regard to localized vascular NCs, old gross infarcts and old microinfarcts were found with about the same frequency across groups (15%–17% for old gross infarcts, 25%–33% for old microinfarcts) while hemorrhages and acute/subacute localized vascular lesions were found relatively less frequently (< 10%); there were no obvious patterns with regard to vascular lesions across LATE-NC stages and none of the preselected comparisons between stages were statistically significant (Table S1). Last, gross hippocampal and cortical atrophy were more common in those with LATE-NC and appeared to increase in frequency with LATE-NC stage. We show the degree of missingness of the different outcome variables in Table S1, which was generally low (< 5%).

3.2 | Associations of LATE-NC stages with clinical diagnoses and other NCs

Associations of LATE-NC stages with clinical diagnosis and other NCs are shown in Figure 2 and Table 2. All LATE-NC stages, including stage 1 subtypes, were associated with increased odds of cognitive impairment, dementia, and memory impairment, compared to those without LATE-NC, though stage 1b only trended toward significance for cognitive impairment ($p = 0.11$). Advancing LATE-NC stages were associated with increasing odds of cognitive impairment (stage 1a odds ratio [OR] = 2.6, stage 1b OR = 2.1, stage 2 OR = 14.3, stage 3 OR = 18.7), dementia (stage 1a OR = 3.1, stage 1b OR = 3.6, stage 2 OR = 8.4, stage 3 OR = 17.9), and memory impairment (stage 1a OR = 3.1, stage 1b OR = 5.7, stage 2 OR = 8.0, stage 3 OR = 11.8). Stage 1a and 1b largely had similar associations with these cognitive outcomes.

With regard to other NCs, LATE-NC was strongly related to HS-A, with odds ratios rising dramatically with stage (stage1a OR = 2.2, stage 1b OR = 7.3, stage 2 OR = 10.4, stage 3 OR = 38.2). Increasing LATE-NC stage was also associated with increasing odds of ADNC (stage 1a OR = 2.8, stage 2 OR = 3.4, stage 3 OR = 5.0), except for stage 1b, which was not associated with ADNC (OR = 1.2, $p = 0.7$). For LBs, stages 1a, 2, and 3 were similarly associated with increased odds of LBs (ORs between 2.5 and 3.1, $p < 0.001$ for all), but stage 1b was not and even weakly trended toward lower odds of LBs (OR = 0.6, $p = 0.19$). LATE-NC stages 1a and 1b were not significantly associated with global vascular NCs, with stage 1b even trending toward lower odds of atherosclerosis (OR = 0.5, $p = 0.088$). LATE-NC stage 2 showed weak associations with increased odds for each of the global vascular NCs (CAA OR = 1.3, $p = 0.055$; atherosclerosis OR = 1.3, $p = 0.061$; arteriolosclerosis OR = 1.5, $p = 0.010$), while stage 3 was more strongly associated with increased odds of CAA (OR = 2.4, $p = 0.002$) and arteriolosclerosis (OR = 2.7, $p = 0.002$), but not atherosclerosis (OR = 1.2, $p = 0.5$). Concerning gross atrophy, there was a steady increase in the odds of moderate or severe hippocampal atrophy with increasing LATE-NC stage (stage 1a OR = 2.0, stage 1b OR = 1.9, stage 2 OR = 3.3, stage 3 OR = 6.6). LATE-NC stage 1a (OR = 1.8, $p = 0.009$), stage 2 (OR = 2.1, $p < 0.001$), and stage 3 (OR = 2.3, $p = 0.006$) were similarly and significantly associated with increased odds of cortical atrophy, but stage 1b was not (OR = 1.2, $p = 0.7$). Only LATE-NC stage 2 was significantly associated with increased odds of frontal/temporal lobar atrophy (OR = 1.8, $p = 0.010$). With regard to localized vascular lesions, none of the LATE-NC stages were significantly or trending toward being related to any of them ($p > 0.1$ for all, data not shown) and were dropped from Figure 1, Table 2, and further analyses.

Post hoc comparisons for associations with clinical diagnoses and other NCs between the different LATE-NC stages are shown in Table 3. General trends for increasing odds with increasing LATE-NC stage generally held, with stage 1 subtypes remaining mostly similar, even if many of these comparisons were not statistically significant. However, the category with the most noticeable deviations from this trend was that of degenerative NCs with respect to stage 1b. Because the deviations were mainly related to LATE-NC stage 1b, in the following text we report ORs for LATE-NC stage 1b with respect to stages 1a and 2; thus, results for the odds comparing stage 1b to stage 2 are inverted as compared to Table 3 (where they are presented as "odds of stage 2 compared to stage 1b"). LATE-NC stage 1b was associated with significantly higher odds of HS-A compared to stage 1a (i.e., "1a vs. 1b," OR = 3.3,

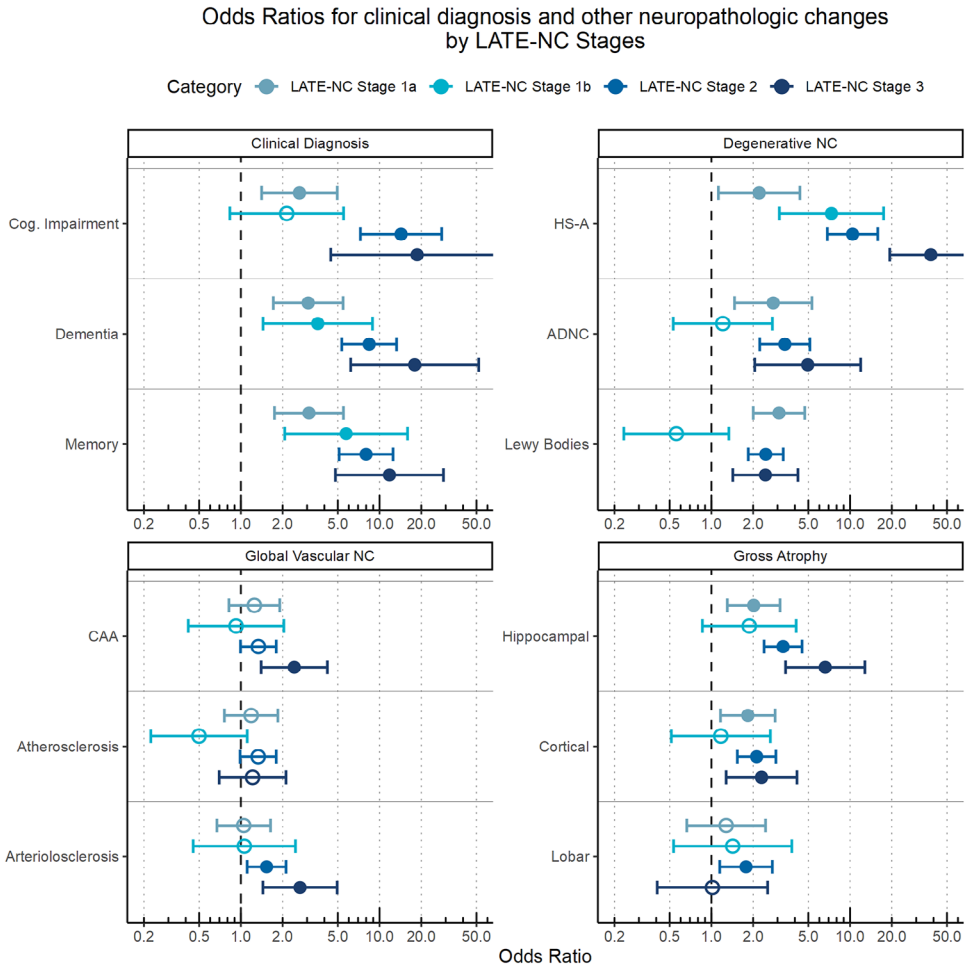

FIGURE 2 Results from logistic regressions for clinical diagnosis and other NCs by LATE-NC stages. Logistic regressions were adjusted for age at death, sex, education, the interval between the last visit and death, and varying intercepts for center. Dots represent odds ratios and error bars represent 95% confidence intervals. Open circles denote $p > 0.05$. The thick vertical dashed line represents odds ratio = 1. ADNC, Alzheimer's disease neuropathologic change; CAA, cerebral amyloid angiopathy; HS-A, hippocampal sclerosis of aging; LATE-NC, limbic-predominant age-related TAR DNA-binding protein of 43 kDa encephalopathy neuropathologic change; NC, neuropathologic changes.

$p = 0.02$), which was fairly comparable to stage 2 (2 vs. 1b, OR = 0.7, $p = 0.4$). LATE-NC stage 1b was associated with lower odds of ADNC with respect to both stage 1a (OR = 0.4, $p = 0.11$) and stage 2 (OR = 0.4, $p = 0.023$), while stages 1a and 2 were similar in this regard (1a vs. 2, OR = 1.2, $p = 0.6$). LATE-NC stage 1b was associated with dramatically lower odds of LBs compared to stage 1a (OR = 0.2, $p < 0.001$) and stage 2 (OR = 0.2, $p = 0.001$). LATE-NC stage 1b was also associated with lower odds of atherosclerosis compared to stage 1a (OR = 0.4, $p = 0.057$) and stage 2 (OR = 0.4, $p = 0.020$).

We investigated associations between LATE-NC stages and NCs with more than two levels using ordinal logistic regressions and the results for these analyses are shown in Figure S2 and Table S2 in supporting information. These were largely similar to the findings using the dichotomized variables, though some of the discrepancies observed using the dichotomized versions of the variables were less pronounced when examining the ordinal versions, such as the strength of the trends for stage 1b relative to the other stages for ADNC and atherosclerosis. From post hoc tests for these ordinal models (Table S3 in supporting information), while the differences between stages 1a and 1b were no longer significant for ADNC and atherosclerosis, they trended for significance for the comparison between 1b and 2 for both ("1b vs 2", ADNC, OR = 2.1, $p = 0.065$; atherosclerosis, OR = 1.8, $p = 0.09$). Furthermore, with the ordinal models, the divergence of the association of stage 1b with CAA became more noticeable (1a vs. 1b, OR = 0.6, $p = 0.13$; 2 vs. 1b, OR = 0.5, $p = 0.033$). We show associations of LATE-NC stages with LB subtypes in Figure S3 and Table S4 in supporting information, in which results were consistent with those from the dichotomized LB variable. Estimates for LATE-NC stage 1b were consistent with lower odds, and other stages (1a, 2, and 3) were consistent with increased odds of amygdala, limbic, and neocortical LBs. None of the LATE-NC stages were associated with olfactory bulb/brainstem LBs. Results from post hoc tests for the LB subtypes (Table S5 in supporting information) showed that stages 1a, 2, and 3 did not differ much in their associations with the LB subtypes, while stage 1b significantly differed from the other stages for amygdala (1a vs. 1b, OR = 0.1, $p = 0.008$; 2 vs. 1b, OR = 0.2, $p = 0.015$), limbic (1a vs. 1b, OR = 0.2,

TABLE 2 Clinical diagnosis and other NCs by LATE-NC stages.

	LATE-NC Stage 1a			LATE-NC Stage 1b			LATE-NC Stage 2			LATE-NC Stage 3		
Variable	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Clinical diagnosis												
Cognitive impairment	2.6	1.4, 5	0.002	2.1	0.8, 5.5	0.114	14.3	7.3, 28.1	<0.001	18.7	4.4, 78.4	<0.001
Dementia	3.1	1.7, 5.5	<0.001	3.6	1.4, 8.9	0.006	8.4	5.3, 13.3	<0.001	17.9	6.2, 51.9	<0.001
Memory	3.1	1.7, 5.5	<0.001	5.7	2.1, 15.9	<0.001	8.0	5.1, 12.5	<0.001	11.8	4.8, 28.9	<0.001
Degenerative NC												
HS-A	2.2	1.1, 4.3	0.022	7.3	3.1, 17.5	<0.001	10.4	6.9, 15.8	<0.001	38.2	19.3, 75.6	<0.001
ADNC	2.8	1.5, 5.3	0.002	1.2	0.5, 2.8	0.652	3.4	2.2, 5.1	<0.001	5.0	2.1, 11.9	<0.001
LBs	3.1	2, 4.7	<0.001	0.6	0.2, 1.3	0.191	2.5	1.8, 3.3	<0.001	2.5	1.4, 4.2	0.001
Global vascular NC												
CAA	1.3	0.8, 1.9	0.300	0.9	0.4, 2	0.843	1.3	1, 1.8	0.055	2.4	1.4, 4.2	0.002
Atherosclerosis	1.2	0.8, 1.8	0.452	0.5	0.2, 1.1	0.088	1.3	1, 1.8	0.061	1.2	0.7, 2.1	0.492
Arteriolosclerosis	1.0	0.7, 1.6	0.836	1.1	0.5, 2.5	0.896	1.5	1.1, 2.1	0.010	2.7	1.4, 4.9	0.002
Gross atrophy												
Hippocampal	2.0	1.3, 3.1	0.002	1.9	0.9, 4.1	0.113	3.3	2.4, 4.5	<0.001	6.6	3.4, 12.8	<0.001
Cortical	1.8	1.2, 2.9	0.009	1.2	0.5, 2.7	0.709	2.1	1.5, 2.9	<0.001	2.3	1.3, 4.1	0.006
Lobar	1.3	0.7, 2.5	0.463	1.4	0.5, 3.8	0.480	1.8	1.1, 2.7	0.010	1.0	0.4, 2.5	0.971

Note: Logistic regressions adjusted for age at death, sex, education, the interval between last visit and death, and varying intercept for center.
Abbreviations: ADNC, Alzheimer's disease neuropathologic change; CAA, cerebral amyloid angiopathy; CI, confidence interval; HS-A, hippocampal sclerosis of aging; LATE-NC, limbic-predominant age-related TAR DNA-binding protein of 43 kDa encephalopathy neuropathologic change; LB, Lewy bodies; NC, neuropathologic change; OR, odds ratio.

TABLE 3 Post hoc tests of clinical diagnosis and other NCs for comparisons between LATE-NC stages.

	1a vs.1b			1a vs.2			1b vs.2			2 vs.3		
Variable	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Clinical diagnosis												
Cognitive impairment	0.8	0.3, 2.4	0.707	5.4	2.3, 13	<0.001	6.7	2.2, 20.6	<0.001	1.3	0.3, 6.2	0.737
Dementia	1.2	0.4, 3.3	0.766	2.8	1.4, 5.4	0.004	2.3	0.9, 6.2	0.086	2.1	0.7, 6.5	0.185
Memory	1.9	0.6, 5.8	0.289	2.6	1.3, 5.1	0.006	1.4	0.5, 4.1	0.546	1.5	0.6, 3.8	0.427
Degenerative NC												
HS-A	3.3	1.2, 9.2	0.021	4.7	2.5, 9.1	<0.001	1.4	0.6, 3.4	0.424	3.7	1.9, 6.9	<0.001
ADNC	0.4	0.2, 1.2	0.107	1.2	0.6, 2.5	0.602	2.8	1.2, 6.8	0.023	1.5	0.6, 3.7	0.426
LBs	0.2	0.1, 0.5	<0.001	0.8	0.5, 1.3	0.356	4.4	1.8, 10.8	0.001	1.0	0.6, 1.8	0.983
Global vascular NC												
CAA	0.7	0.3, 1.8	0.497	1.1	0.7, 1.7	0.777	1.4	0.6, 3.3	0.375	1.8	1, 3.2	0.043
Atherosclerosis	0.4	0.2, 1	0.057	1.1	0.7, 1.8	0.635	2.7	1.2, 6.1	0.020	0.9	0.5, 1.6	0.757
Arteriolosclerosis	1.0	0.4, 2.6	0.984	1.5	0.9, 2.4	0.133	1.4	0.6, 3.5	0.409	1.7	0.9, 3.3	0.094
Gross atrophy												
Hippocampal	0.9	0.4, 2.2	0.869	1.6	1, 2.6	0.048	1.8	0.8, 3.9	0.174	2.0	1, 4	0.046
Cortical	0.6	0.3, 1.6	0.336	1.2	0.7, 1.9	0.561	1.8	0.8, 4.2	0.170	1.1	0.6, 2	0.795
Lobar	1.1	0.4, 3.5	0.852	1.4	0.7, 2.8	0.358	1.2	0.4, 3.5	0.673	0.6	0.2, 1.5	0.251

Note: Logistic regressions were adjusted for age at death, sex, education, the interval between the last visit and death, and varying intercepts for center.
Abbreviations: ADNC, Alzheimer's disease neuropathologic change; CAA, cerebral amyloid angiopathy; CI, confidence interval; HS-A, hippocampal sclerosis of aging; LATE-NC, limbic-predominant age-related TAR DNA-binding protein of 43 kDa encephalopathy neuropathologic change; LB, Lewy bodies; MCI, mild cognitive impairment; NC, neuropathologic changes; OR, odds ratio.

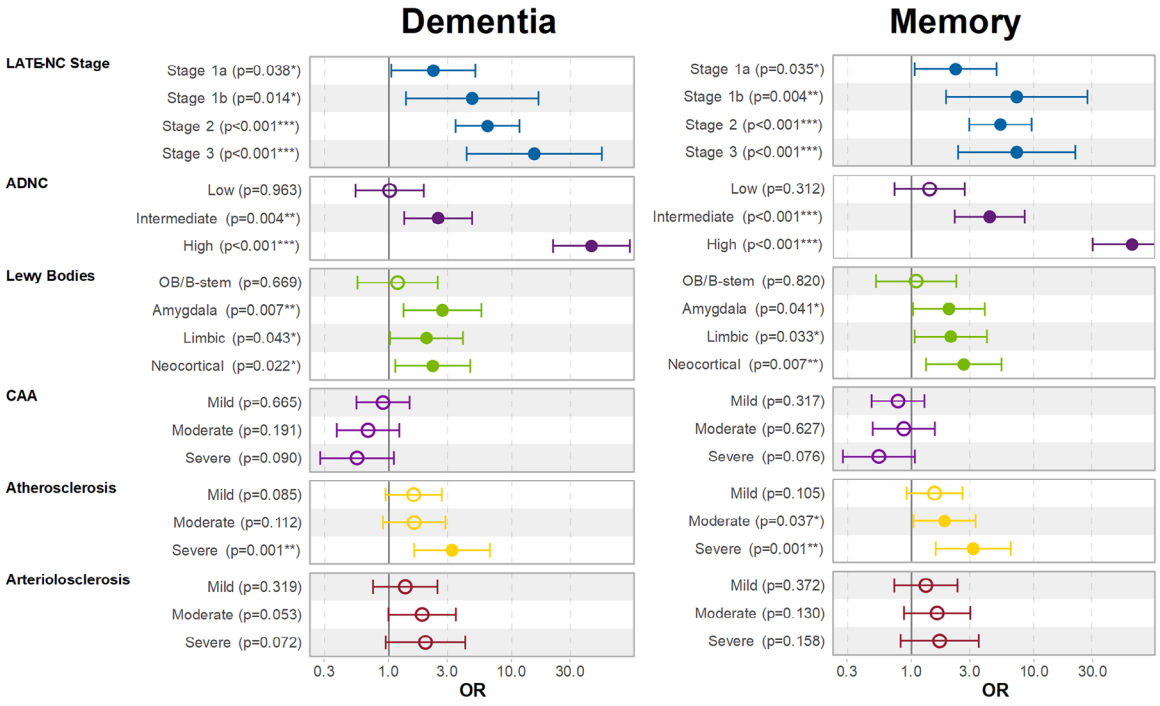

FIGURE 3 Results from logistic regressions of dementia and memory impairment for LATE-NC stages and related NCs. Logistic regressions were adjusted for age at death, sex, education, the interval between the last visit and death, and varying intercepts for center. Dots represent odds ratios and error bars represent 95% confidence intervals. Open circles denote $p > 0.05$. The thick vertical solid line represents odds ratio = 1. ADNC, Alzheimer's disease neuropathologic change; CAA, cerebral amyloid angiopathy; LATE-NC, limbic-predominant age-related TAR DNA-binding protein of 43 kDa encephalopathy neuropathologic change; NCs, neuropathologic changes; OB/B-stem, olfactory bulb or brainstem; OR, odds ratio.

$p = 0.042$; 2 vs. 1b, OR = 0.2, $p = 0.070$), and neocortical (1a vs. 1b, OR = 0.1, $p = 0.029$; 2 vs. 1b, OR = 0.1, $p = 0.037$) LBs.

3.3 | Associations of LATE-NC stages with clinical diagnoses while accounting for other NCs

Last, we examined the association of LATE-NC stages with the outcomes of dementia and memory impairment while accounting for the other NCs. Because of the strong and likely causal association between LATE-NC and HS-A, we excluded HS-A from these models. We show the results for these models in Figure 3 and Table 4. We excluded 79 participants (5.8% of the total) from this analysis due to missing data on one or more of the variables. We found that all LATE-NC stages, even stage 1 subtypes, were significantly associated with dementia and memory impairment. In fact, estimates for the OR of dementia for LATE-NC stage 1a was 2.3, comparable to the largest effects of other non-ADNC pathologies and similar to the OR = 2.5 for moderate likelihood ADNC. LATE-NC stages 1b (OR = 4.8), 2 (OR = 6.4) and 3 (OR = 15.3) showed strong associations for increased odds of dementia, surpassed only by high likelihood ADNC (OR = 44.5). With regard to memory, LATE-NC stage 1a was significantly associated with increased odds of memory impairment (OR = 2.3), while stages 1b, 2, and 3, showed similar odds of memory impairment (OR ≈ 7), stronger than those of any other NC level except for high likelihood ADNC (OR = 64.5). Analyses using ordinal logistic regressions across the levels of cognitive status and CDR memory scores showed similar results (Figure S4 and Table S6 in supporting information).

4 | DISCUSSION

In this study, we evaluated the updated LATE-NC staging criteria using data from participants in NACC. We assigned LATE-NC stages, including stage 1 subtypes, using regional TDP-43 assessments from the amygdala, hippocampus, and neocortex. LATE-NC was present in 37% of participants (29% stage 1, 58% stage 2, 13% stage 3). While most participants with stage 1 LATE-NC were 1a (78%), stage 1b was fairly common (22%). All LATE-NC stages were significantly associated with cognition, HS-A, and hippocampal atrophy. Within LATE-NC stage 1 subtypes, stage 1a and 1b were similarly, and less strongly than stage 2, associated with worse cognition. However, stage 1b diverged from other stages as it was not associated with ADNC or LBs, but compared to stage 1a was associated with older age and HS-A. When accounting for other NCs, all LATE-NC stages were significantly associated with higher odds of dementia and memory impairment, and the effects of stages 1b, 2, and 3 were only surpassed by those of high ADNC.

The 37% of participants with LATE-NC in our sample is similar to the 39% obtained from pooling data across participants from 13 large community cohorts, many of which do not contribute data to NACC.[27] We

TABLE 4 Dementia and memory impairment concerning LATE-NC stages, related NCs, and demographic variables.

	Logistic regression, dementia			Logistic regression, memory		
Characteristic	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Age at death (*z* score)	0.69	0.54, 0.87	0.002	0.69	0.54, 0.87	0.002
Sex						
Female	—	—		—	—	
Male	1.38	0.94, 2.03	0.10	1.42	0.97, 2.10	0.073
Years of education (*z* score)	0.80	0.67, 0.97	0.025	0.79	0.66, 0.96	0.018
Visit to death (*z* score)	0.73	0.60, 0.90	0.003	0.67	0.55, 0.83	<0.001
LATE-NC stage						
No TDP-43	—	—		—	—	
Stage 1a	2.30	1.05, 5.06	0.038	2.30	1.06, 4.98	0.035
Stage 1b	4.77	1.38, 16.5	0.014	7.29	1.92, 27.7	0.004
Stage 2	6.36	3.49, 11.6	<0.001	5.36	2.98, 9.65	<0.001
Stage 3	15.3	4.30, 54.1	<0.001	7.29	2.41, 22.0	<0.001
ADNC						
Not	—	—		—	—	
Low	1.02	0.54, 1.92	>0.9	1.41	0.73, 2.73	0.3
Intermediate	2.52	1.33, 4.76	0.004	4.38	2.26, 8.47	<0.001
High	44.5	21.7, 91.5	<0.001	64.3	30.5, 135	<0.001
LB						
None	—	—		—	—	
OB/B-stem	1.18	0.56, 2.50	0.7	1.09	0.51, 2.33	0.8
Amygdala	2.73	1.32, 5.66	0.007	2.03	1.03, 3.99	0.041
Limbic	2.02	1.02, 4.00	0.043	2.10	1.06, 4.15	0.033
Neocortical	2.28	1.13, 4.83	0.022	2.68	1.32, 5.47	0.007
CAA						
None	—	—		—	—	
Mild	0.90	0.54, 1.47	0.7	0.78	0.47, 1.28	0.3
Moderate	0.68	0.38, 1.22	0.2	0.86	0.48, 1.55	0.6
Severe	0.55	0.28, 1.10	0.090	0.54	0.27, 1.07	0.076
Atherosclerosis						
None	—	—		—	—	
Mild	1.59	0.94, 2.69	0.085	1.55	0.91, 2.62	0.11
Moderate	1.61	0.89, 2.89	0.11	1.87	1.04, 3.35	0.037
Severe	3.27	1.61, 6.64	0.001	3.21	1.58, 6.51	0.001
Arteriolosclerosis						
None	—	—		—	—	
Mild	1.36	0.74, 2.49	0.3	1.31	0.72, 2.38	0.4
Moderate	1.86	0.99, 3.51	0.053	1.62	0.87, 3.03	0.13
Severe	1.98	0.94, 4.18	0.072	1.70	0.81, 3.56	0.2

Note: Logistic regressions were adjusted for age at death, sex, education, the interval between last visit and death, and varying intercepts for center.
Abbreviations: ADNC, Alzheimer's disease neuropathologic change; CAA, cerebral amyloid angiopathy; CI, confidence interval; HS-A, hippocampal sclerosis of aging; LATE-NC, limbic-predominant age-related TDP-43 encephalopathy neuropathologic change; LB, Lewy bodies; MCI, mild cognitive impairment; NC, neuropathologic changes; OB/B-stem, olfactory bulb or brainstem; OR, odds ratio; TDP-43, TAR DNA-binding protein of 43 kDa.

found LATE-NC stages to be significantly associated with older ages at death and higher frequency of dementia, memory impairment, and presence of an *APOE* ε4 allele, similar to previous studies.[7,27,28] Those with LATE-NC stages 1 and 2 had a higher frequency of having been assessed using a phospho-specific TDP-43 antibody, which may indicate that phospho-specific antibodies provide a detection benefit for TDP-43 pathology in these early stages. However, the type of TDP-43 antibody used was mostly consistent within each ADRC, and thus this finding may be partially related to other center-specific effects.

Similar to previous studies, we found LATE-NC to be most strongly associated with HS-A[29–31] but also significantly associated with ADNC[27,32] and LBs.[27,33] While a previous study found only neocortical LBs to be associated with advanced stage (2+) LATE-NC,[33] which concurs with our findings of LATE-NC being associated with neocortical LBs but not with olfactory bulb/brainstem LBs, we also found that LATE-NC was associated with limbic and amygdala-predominant LBs. LATE-NC stage 2 was weakly associated with CAA, atherosclerosis, and arteriolosclerosis, while stage 3 was more strongly related to CAA and arteriolosclerosis but not atherosclerosis. None of the LATE-NC stages were associated with localized vascular lesions. These findings are consistent with previous reports[34] in which, across multiple cohorts and analyses, LATE-NC was not found to be associated with localized vascular lesions while it was associated with global vascular NCs such as arteriolosclerosis. Given the variation in regional occurrence of these vascular lesions, future studies should examine associations of LATE-NC with more regionally specific measures of vascular lesion burden. Hippocampal atrophy was significantly and strongly associated with LATE-NC, consistent with previous studies.[35–37] To what degree LATE-NC–related hippocampal atrophy might be driven by HS-A, which has also been shown to be strongly associated with both hippocampal atrophy[37–40] and LATE-NC, is beyond the scope of this study but is an important future research question. Gross cortical atrophy showed a weaker but consistent effect across LATE-NC stages, which tracks with eventual involvement of the cortex in LATE-NC.[36,41]

Previous LATE-NC staging schemes, such as those from Josephs et al.,[42,43] Nag et al.,[30,44] and the original LATE-NC consensus paper,[7] held the amygdala as the first, and ubiquitous, region to be involved. A recent data-driven staging study of ALS-TDP, FTLD-TDP, and LATE-NC[45] restricted classifying LATE-NC to those with at least amygdala TDP-43 pathology. However, previous studies and reports have noted cases in which TDP-43 is found in the amygdala but not the hippocampus.[10,46,47] In one of the studies by Nag et al.[30] they reported 18 cases, or 3% of all of those with LATE-NC, in which skipping of regions seemed to have occurred, even after additional sampling was performed, and the most common finding ($n = 8$) was lack of amygdala TDP-43. These findings prompted the updated LATE-NC staging criteria, including stage 1 subtypes, which we examined in this study.

For both LATE-NC stage 1a and 1b we found similar frequencies (but lower than stage 2) of cognitive impairment, dementia, and memory impairment. We also observed a significantly older age at death for those with stage 1b compared to 1a. LATE-NC stage 1a was more closely associated with a general deposition of misfolded pathological proteins, both ADNC and LB, while stage 1b was strongly associated with HS-A but was not associated with ADNC or LB. This may relate to specific subtypes of TDP-43 in LATE-NC[9] or different patterns in amygdala TDP-43 types.[10] We also take these results to suggest that LATE-NC stage 1b is indeed part of the LATE-NC spectrum, as opposed to the ALS/FTLD-TDP spectrum, because (1) participants with stage 1b tended to be older at death; (2) we limited the sample to participants without impairment or with impairment of the AD type and we excluded not only participants with ALS/FTLD-TDP pathologically[48] but also those with clinical syndromes of FTD; (3) ADNC was still quite common in stage 1b, comparable to the reference group which itself is enriched for ADNC; and (4) isolated hippocampal TDP-43 is rare in ALS/FTLD-TDP (≈ 2% in a previous study[4]). We believe these findings support stage 1 subtyping for LATE-NC.

Taken together, these results suggest that some NCs, such as HS-A, and autopsy findings, such as atrophy, are downstream of LATE-NC as evidenced by the strong associations, dose-response across stages, and biological plausibility.[34] Meanwhile, associations of LATE-NC and ADNC may reflect upstream genetic and/or pathological risk factors such as *APOE* and amyloid,[34] but may also potentially reflect a degree of synergy in the pathological spread between TDP-43 and tau.[49,50] With regard to differences between LATE-NC stages 1a and 1b, the vulnerability/resistance of the amygdala seems to be key. A common site for the accumulation of misfolded proteins,[51] previous imaging studies have reported amygdala atrophy related to LATE-NC, HS-A, ADNC, and LBs.[35,52] The fact that participants with LATE-NC stage 1b were also less likely to have ADNC and amygdala/limbic LBs may suggest a degree of resilience to the accumulation of NCs in the amygdala which may offset TDP-43 accumulation in this region but which then eventually starts in the hippocampus. Last, associations between LATE-NC and global vascular pathologies may relate to similar upstream blood–brain barrier dysfunction, or the blood–brain barrier dysfunction caused by global vascular pathologies may increase the risk of developing LATE-NC.[34]

We found LATE-NC stages, even stage 1 subtypes, were associated with worse cognitive status and memory impairment while accounting for other NCs, and LATE-NC stages 1b, 2, and 3 were associated with higher odds of dementia than any other level of other NCs except for high ADNC. Previous studies have shown consistent associations of LATE-NC with cognitive decline even when accounting for other NCs, with several studies showing similar magnitude of effects for LATE-NC and ADNC.[5,53] While some previous studies have reported a limited impact of LATE-NC stage 1 on cognition,[7,44,54] using the new staging criteria and a large sample size limited to those without impairment or with impairment of the AD type, we found that stage 1 was significantly associated with both dementia and memory impairment, though these associations were weaker than for the other stages. Together, these results suggest that the effects of LATE-NC on cognition and memory are strong and independent of other common NCs, with significant associations for even low stages and stronger associations at later stages. Thus, within the spectrum of dementia of the AD type, LATE-NC and ADNC contribute considerably and independently to dementia and memory impairment.

4.1 | Limitations

The main limitation of this study is the inability to apply the updated LATE-NC staging criteria[12] in a strict sense to the NACC data. However, we implemented the updated LATE-NC staging criteria as best could be applied to the NACC dataset. Another limitation is that NACC participants are not representative of the general population as each ADRC has its own recruitment criteria, leading to a higher frequency of participants with dementia, but also differences across specific NCs.[55] However, we tried to limit the sample to that most relevant for LATE-NC by excluding participants with certain NCs (such as FTLD-TDP[48]) and/or with non-AD etiologic diagnosis, with the aim of excluding those with TDP-43 related to other NCs. The choice of using data from participants with AD etiologic diagnosis or without impairment does not guarantee neuropathological homogeneity and may limit the potential applicability of the findings to other conditions such as in vascular and LB dementia, but does provide a more syndromically homogeneous validation cohort for the updated LATE-NC criteria. The lack of representativeness in NACC also extends to racial and ethnic diversity,[56] and while some studies have found similar rates of LATE-NC in historically marginalized racial and ethnic groups,[57,58] conducting studies of LATE-NC in diverse cohorts must be a priority for the field.

4.2 | Conclusion

The updated LATE-NC staging criteria captures variations in early patterns of TDP-43 spread, through stage 1 subtypes, which are consequential for associations with cognition and other NCs.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to report. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

NACC data are publicly available upon request.

CONSENT STATEMENT

Each Alzheimer's Disease Research Center that contributes to the National Alzheimer's Coordinating Center database is approved by their local institutional review board and each collects written informed consent from all participants and co-participants.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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